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Proteinuria and hematuria after remission induction are associated with outcome in ANCA-associated vasculitis

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In anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV), hematuria and proteinuria are biomarkers reflecting kidney involvement at diagnosis. Yet, the prognostic value of their persistence after immunosuppressive induction therapy, reflecting kidney damage or persistent disease, remains uncertain. To study this, our post hoc analysis included participants of five European randomized clinical trials on AAV (MAINRITSAN, MAINRITSAN2, RITUXVAS, MYCYC, IMPROVE). Urine protein-creatinine ratio (UPCR) and hematuria of spot urine samples collected at the end of induction therapy (four-six months after treatment initiation) were correlated with the occurrence of a combined end point of death and/or kidney failure, or relapses during follow-up. Among 571 patients (59% men, median age 60), 60% had anti–proteinase 3-ANCA and 35% had anti–myeloperoxidase-ANCA, while 77% had kidney involvement. After induction therapy, 157/526 (29.8%) had persistent hematuria and 165/481 (34.3%) had UPCR of 0.05 g/mmol or more. After a median follow-up of 28 months (interquartile range 18-42), and adjustment for age, ANCA type, maintenance therapy, serum creatinine and persistent hematuria after induction, a UPCR of 0.05 g/mmol or more after induction was associated with significant risk of death/kidney failure (adjusted Hazard Ratio [HR] 3.06, 95% confidence interval 1.09-8.59) and kidney relapse (adjusted subdistribution HR 2.22, 1.16-4.24). Persistent hematuria was associated with significant kidney relapse (adjusted subdistribution HR 2.16, 1.13-4.11) but not with relapse affecting any organ nor with death/kidney failure. Thus, in this large cohort of patients with AAV, persistent proteinuria after induction therapy was associated with death/kidney failure and kidney relapse, whereas persistent hematuria was an independent predictor of kidney relapse. Hence, these parameters must be considered to assess long-term kidney prognosis of patients with AAV.

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Anti-neutrophil cytoplasm antibody (ANCA)–associated vasculitides (AAVs) are a group of small vessel necrotizing vasculitis syndromes with multisystemic involvement, including the kidney.[1] Notwithstanding the significant progress achieved during these last decades regarding induction and maintenance immunosuppressive therapy,[2–5] severe organ damage due to delayed diagnosis[6] remains a major concern for patients with AAV.

Kidney involvement in AAV is characterized by pauci-immune necrotizing crescentic glomerulonephritis. The occurrence of glomerulonephritis is particularly frequent in microscopic polyangiitis and granulomatosis with polyangiitis, affecting >50% of all patients at diagnosis or during follow-up and sometimes leading to chronic kidney disease (CKD), which is independently associated with poor survival.[7,8] Kidney failure can result from irreversible initial acute kidney disease or occur years later because of the nonspecific progression of CKD or to vasculitis relapses.[9]

At AAV diagnosis, hematuria and proteinuria are considered as biomarkers reflecting kidney involvement.[10] Yet, the prognostic value of their persistence after the induction of remission by immunosuppressive therapy remains uncertain,

Lay Summary

Anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitides are small vessels necrotizing diseases with multisystemic involvement, including the kidney. Hematuria and proteinuria are biomarkers reflecting kidney involvement at diagnosis. Yet, the prognostic value of their persistence after immunosuppressive induction therapy, reflecting either kidney damage or persistent disease, remains uncertain. In this *post hoc* study including 571 participants (77% of whom had kidney involvement) of 5 European randomized clinical trials on ANCA-associated vasculitis, the prognostic value of urine protein-creatinine ratio (UPCR) and hematuria of spot urine samples collected at the end of induction therapy was studied. After induction therapy, 29.8% of patients had persistent hematuria and 34.3% had UPCR ≥0.05 g/mmol. After a median follow-up of 28 months and adjustment for age, ANCA type, maintenance therapy, serum creatinine, proteinuria and hematuria, persistence of a UPCR ≥0.05 g/mmol after induction therapy was associated with poorer kidney survival and increased risk of kidney relapse whereas persistent hematuria was an independent predictor of kidney relapse. These parameters must be taken into account to assess the long-term renal prognosis of patients with ANCA–associated vasculitis.

although it could reflect either kidney damage or persistent active disease.

Albuminuria excretion rate,[11–13] and by extension proteinuria excretion rate,[14,15] is a well-recognized predictive factor for kidney failure in the general population and especially in patients with glomerular diseases.[16,17] However, in AAV, its persistence after induction therapy has seldom been investigated, and no study has demonstrated a prognostic value for this simple biomarker. In contrast, a recent study has suggested that persistent hematuria during the remission phase of AAV is associated with the subsequent risk of kidney relapse but not with the risk of progression to kidney failure.[18]

The aim of this study was to evaluate the prognostic value of persistent proteinuria and/or hematuria after induction therapy in a large population of patients with AAVs by using pooled individual participant data from 5 large randomized controlled trials.

METHODS

Setting/participants

This study was a *post hoc* individual patient data analysis from 5 international multicenter randomized controlled trials on AAV published between 2010 and 2019. The Efficacy Study of Two Treatments in the Remission of Vasculitis (MAINRITSAN) and Comparison Study of Two Rituximab Regimens in the Remission of ANCA Associated Vasculitis (MAINRITSAN2) trials were coordinated by the French Vasculitis Study group, whereas RITUXVAS (An international, randomised, open label trial comparing a rituximab-based regimen with a standard cyclophosphamide/azathioprine based regimen in the treatment of active, generalised anti-neutrophilic cytoplasmic antibodies associated vasculitis), Clinical Trial of Mycophenolate Versus Cyclophosphamide in ANCA Vasculitis (MYCYC), and Mycophenolate Mofetil Versus Azathioprine for Maintenance Therapy in ANCA Associated Systemic Vasculitis (IMPROVE) were performed by the European Vasculitis Society network. Rationale, study design, and results of these studies have been published elsewhere,[3,19–22] and their main characteristics are presented in Supplementary Tables S1 and S2. All 5 trials included either newly diagnosed or relapsing patients with granulomatosis with polyangiitis or microscopic polyangiitis (defined by 1994 Chapel Hill nomenclature)[23] and compared different induction or maintenance immunosuppressive therapy schemes. Local ethics committees approved each of the studies, and all patients gave written informed consent for participation.

All adult patients included in these trials were eligible for this study. Patients were excluded from the analysis if death or kidney failure had occurred during induction therapy or if no serum creatinine (sCreat) measurement was available after the end of induction therapy.

Data sources

For patients included in the MAINRITSAN study, we retrospectively contacted investigators to request proteinuria data after induction therapy from individual patient medical file. For the other studies, data were prospectively collected and retrieved in electronic data sets.

We reviewed the individual study protocols, template case report forms, and database dictionaries to harmonize study databases. We updated each database with unified coding across trials and merged them into a single database.

Exposure/definitions

The 2 main variables of interest were (i) proteinuria and (ii) hematuria, collected in a single measurement at the end of induction therapy, that is, between 4 and 6 months after treatment initiation for active disease (onset or flare; details in Supplementary Table S2). Proteinuria was quantitatively measured in either 24-hour urine samples or random spot urine samples, together with urinary creatinine level. Throughout this article, *proteinuria excretion rate* is defined and expressed as urine protein-creatinine ratio (UPCR) in grams per millimole. *Hematuria* was defined by the presence of ≥10 red blood cells per mm^3 in cytological examination of the urine. If cytological urine data were missing, blood by dipstick was used to identify hematuria.

Covariates and definitions

Baseline clinical characteristics (age, sex, ANCA, and AAV type), immunosuppressive therapies, and clinical, biological, and histological data prospectively collected during follow-up visits were analyzed. *Remission* was defined as a Birmingham Vasculitis Activity Score of 0.

Kidney involvement was defined as ≥1 kidney Birmingham Vasculitis Activity Score items present at entry or relapse, excluding hypertension alone (i.e., new or worsening hematuria, red blood cell casts, or new rise in sCreat ≥30%). Kidney function was assessed using sCreat and estimated glomerular filtration rate (eGFR), calculated using the Modified Diet in Renal Disease equation. Histological data, when available, were analyzed by a kidney pathologist at each center, with centralized review for biopsies from the RITUXVAS trial, and Berden classification[24] was retrospectively established.

End points

The main outcomes were time from the end of induction therapy to (i) a composite end point of death or incident kidney failure, whichever occurred first; (ii) first relapse; and (iii) first kidney relapse during follow-up. The secondary outcome included time from the end of induction therapy to (i) a composite end point of death or severe CKD, (ii) incident kidney failure, and (iii) severe CKD.

Incident kidney failure was defined as dialysis dependence at 2 consecutive visits at least 1 month apart or kidney transplantation. *Severe CKD* was defined as eGFR <30 ml/min per 1.73 m^2 (Kidney Disease: Improving Global Outcomes GFR categories G4 or G5) at ≥2 consecutive visits and included kidney failure. *Relapses* were defined as the recurrence or new appearance of any disease activity reflected by a Birmingham Vasculitis Activity Score of >0. *Kidney relapses* were defined as relapses with kidney involvement as defined above.

Statistical analysis

Categorical variables were summarized as number (percentage), and continuous variables were expressed as median (interquartile range [IQR]). To ensure a clear and simple clinical message, UPCR was coded as a binary variable (<0.05 or ≥0.05 g/mmol). The cumulative incidence of the composite outcome of death or kidney failure according to UPCR after induction therapy was determined using the Kaplan-Meier method with the use of the log-rank test. Cox proportional hazards regression models were used to estimate bivariate associations between patients' characteristics (at baseline and after induction therapy) and time to death/kidney failure. In multivariable Cox regression models, the effect of UPCR and hematuria after induction therapy on the composite end points of death or kidney failure and death or severe CKD, were adjusted for age, ANCA type, maintenance therapy, sCreat, UPCR, and hematuria after induction therapy. Patients without the occurrence of the end point were censored at the end of follow-up. Proportional hazards assumptions were graphically tested with Schoenfeld residuals.

For the outcomes of kidney relapse and relapse affecting any organ, incident kidney failure, and severe CKD, competing risk regression was performed.[25] For the outcome of kidney relapse, occurrence of death, kidney failure, and non-kidney relapse were considered competing events. For the outcome of relapse affecting any organ, death and kidney failure were considered competing events. For the outcomes of incident kidney failure and severe CKD, death was considered a competing event. Patients without the occurrence of the end point or any competing event were censored at the end of follow-up. The cumulative incidence of outcomes according to hematuria or UPCR was estimated, and adjusted analyses were performed accounting for age, ANCA type, maintenance therapy, sCreat, and hematuria or UPCR after induction therapy.

The association between risk factors and outcome was expressed as subdistribution hazard ratio (sHR) or hazard ratio (HR) with 95% confidence interval (95% CI). Covariates included in multivariable analyses were selected from among those with $P < 0.05$ in bivariate analyses or those with a known prognostic impact in the literature.

Statistical significance was set at 2-sided$P < 0.05$. Analyses were performed with R Studio software version 1.2.5033 (R Project for Statistical Computing, R Foundation).

Subgroups, sensitivity analysis, and missing data handling

Subgroup analysis including (i) only patients with kidney involvement at baseline, (ii) patients with myeloperoxidase (MPO)–ANCA antibodies, (iii) patients with proteinase 3 (PR3)–ANCA antibodies, and (iv) patients with kidney pathology available at induction therapy initiation was performed.

The complete case method was adopted in the primary statistical analysis. To address missing data, the analysis assessing the time from the end of induction therapy to the composite end point of death or kidney failure was repeated with the entire cohort using the technique of multiple imputations by chained equations. The variables with missing data were imputed using all covariates of interest except those with >20% missing data. Using the "mice" package in R Studio,[26] 5 imputations were performed with 5 iterations per imputation.

Sensitivity analyses were performed using sCreat at induction therapy initiation and delta sCreat (sCreat before minus sCreat after induction) instead of sCreat after induction in the kidney survival models. An additional analysis was performed including ANCA persistence after induction therapy as an additional covariate for relapse-related outcomes. At last, sensitivity analyses with UPCR coded as a continuous variable were implemented.

RESULTS

Study population

Of the 617 patients enrolled in the 5 trials (MAINRITSAN, MAINRITSAN2, RITUXVAS, MYCYC, and IMPROVE),[3,19–22] data were available for 614. After exclusion of 43 participants, 571 were included in the present study (Figure 1).

Baseline characteristics, clinical data, and biological data at the initiation of and after induction therapy are detailed for these 571 patients in Table 1. Briefly, there were 59% men, the median age was 60 years (IQR 50–68 years), 60% had anti–PR3-ANCA, 35% had anti–MPO-ANCA, and 77% had kidney involvement with a median sCreat of 133 μmol/l (IQR 84.3–241.8 μmol/l) at induction therapy initiation. Cyclophosphamide was used for the induction of remission in 75% of cases (63% i.v., 12% orally), rituximab for 15%, and mycophenolate mofetil for 10%. Rituximab and azathioprine were used as maintenance therapy in 37% and 46% of cases, respectively.

At the end of induction therapy, the median UPCR was 0.025 g/mmol (IQR 0.007–0.081 g/mmol), with 34.3% of patients (165 of 481) displaying UPCR ≥0.05 g/mmol. At this time point, persistent hematuria was noted in 29.8% of cases (157 of 526).

Death or kidney failure

After a median follow-up of 28 months (IQR 18–42 months) from the end of induction therapy, the composite outcome of death or kidney failure occurred in 5.1% of patients (29 of 571), including 2.3% of deaths (13 of 571) and 2.8% of incident kidney failure cases (16 of 571).

Factors associated with this outcome in bivariate and multivariable analysis are listed in Table 2. In multivariable analysis, the only factors independently associated with the occurrence of this end point were higher sCreat and UPCR ≥0.05 g/mmol after induction therapy (vs. <0.05 g/mmol: HR 3.06; 95% CI 1.09–8.59; $P = 0.034$; Kaplan-Meier survival curve shown in Figure 2) whereas persistent hematuria was not. UPCR after induction therapy was also

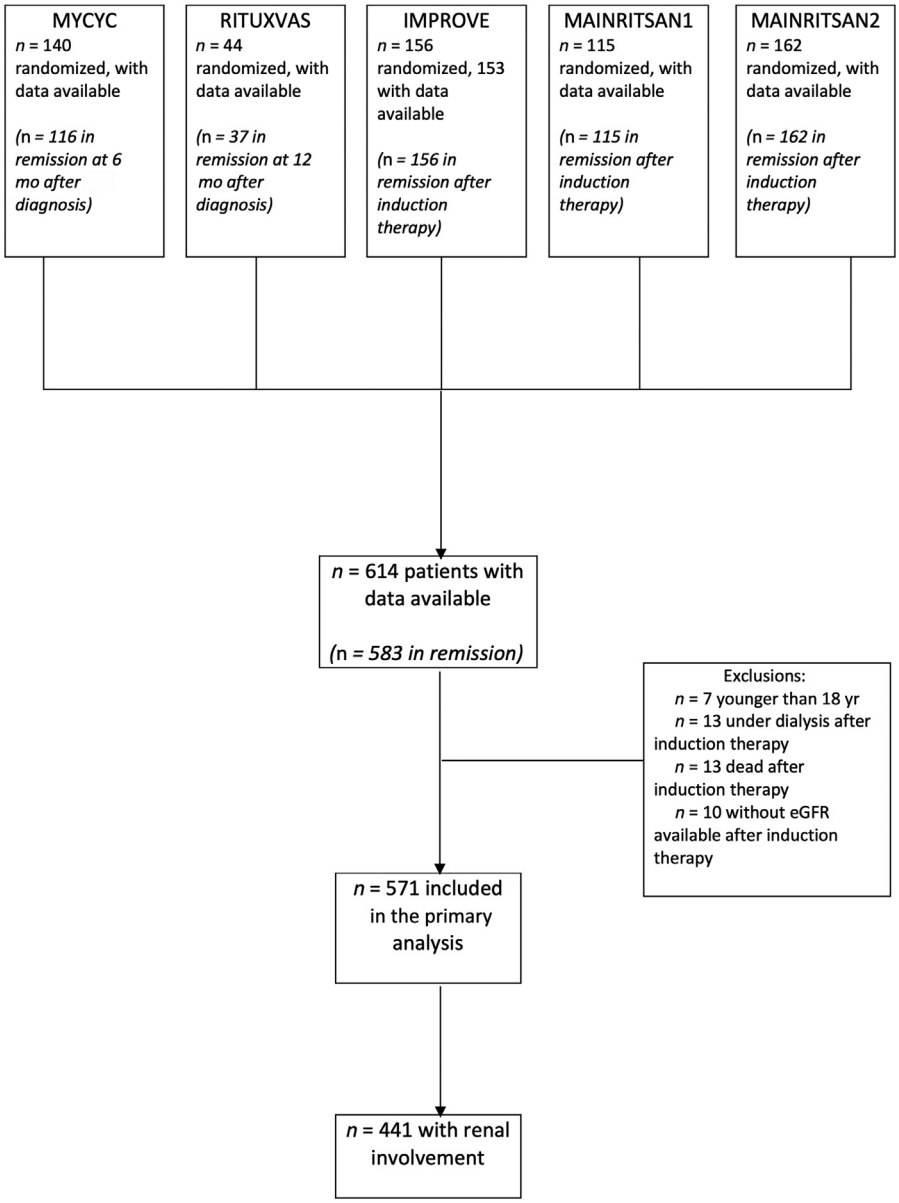

Figure 1 | Flowchart. eGFR, estimated glomerular filtration rate; IMPROVE, Mycophenolate Mofetil Versus Azathioprine for Maintenance Therapy in ANCA Associated Systemic Vasculitis[19]; MAINRITSAN, Efficacy Study of Two Treatments in the Remission of Vasculitis[20]; MAINRITSAN2, Comparison Study of Two Rituximab Regimens in the Remission of ANCA Associated Vasculitis[21]; MYCYC, Clinical Trial of Mycophenolate Versus Cyclophosphamide in ANCA Vasculitis[22]; RITUXVAS, An international, randomised, open label trial comparing a rituximab-based regimen with a standard cyclophosphamide/azathioprine based regimen in the treatment of active, generalised anti-neutrophilic cytoplasmic antibodies associated vasculitis.[3]

independently associated with this outcome when sCreat after induction therapy was replaced by sCreat at induction therapy initiation and by delta sCreat. Overall, there were 12.1% of deaths/kidney failure cases (20 of 165) among patients with UPCR ≥0.05 g/mmol versus 1.6% (5 of 316) among those with UPCR <0.05 g/mmol.

When considering death as a competing event, incident kidney failure occurred more often when UPCR was ≥0.05 g/mmol ($n = 13$ of 165 [7.9%]) than when UPCR was <0.05 g/mmol ($n = 1$ of 316 [0.3%]; cumulative incidence in Supplementary Figure S1).

Death or severe CKD (eGFR <30 ml/min per 1.73 m^2)

The composite outcome of death or severe CKD occurred in 13.7% of patients (78 of 571) after a median follow-up of 28 months (IQR 12–42 months).

In multivariable analysis (Supplementary Table S3), factors associated with this outcome were age, higher sCreat, and UPCR after induction therapy ≥0.05 g/mmol (vs. <0.05 g/mmol: HR 3.85; 95% CI 1.96–7.58; $P < 0.001$).

When considering death as a competing event, severe CKD occurred more often when UPCR was ≥0.05 g/mmol ($n = 46$ of 165 [27.9%]) versus than when UPCR was <0.05 g/mmol

Table 1 | Characteristics at the initiation of and after induction therapy ($N = 571$)

Characteristic	Value
Male sex	336/571 (58.8)
Age, yr	60 (50–68)
ANCA type (ELISA)	
Proteinase 3	318/532 (59.8)
Myeloperoxidase	185/532 (34.8)
Negative	29/532 (5.5)
AAV type	
Granulomatosis with polyangiitis	386/571 (67.6)
Microscopic polyangiitis	185/571 (32.4)
Induction therapy	
i.v. cyclophosphamide	359/571 (62.9)
p.o. cyclophosphamide	70/571 (12.3)
Rituximab	84/571 (14.7)
Mycophenolate mofetil	57/571 (10.0)
Methotrexate	1/571 (0.2)
Maintenance therapy	
Rituximab	212/571 (37.1)
Azathioprine	261/571 (45.7)
Mycophenolate mofetil	71/571 (12.4)
None	27/571 (4.7)
Kidney involvement	441/571 (77.2)
De novo AAV flare (vs. relapse)	495/571 (86.7)
Data at induction therapy initiation	
Serum creatinine, μmol/l[a]	133 (84.8–246.3)
eGFR, ml/min per 1.73 m^2[b]	45 (21–77)
UPCR, g/mmol[c]	0.082 (0.022–0.175)
Hematuria	153/269 (56.9)
Pulmonary involvement	141/270 (52.2)
Intra-alveolar hemorrhage	47/269 (17.5)
Data at the end of induction therapy	
Serum creatinine, μmol/l	105 (88–142)
eGFR, ml/min per 1.73 m^2	58 (40–77)
ANCA positivity	313/534 (58.6)
Hematuria	157/526 (29.8)
UPCR, g/mmol[d]	0.025 (0.007–0.081)
UPCR <0.03 g/mmol[d]	262/480 (54.6)
UPCR 0.03–0.1 g/mmol[d]	117/480 (24.4)
UPCR >0.1 g/mmol[d]	101/480 (21.0)
UPCR <0.05 g/mmol[d]	316/481 (65.7)
UPCR ≥0.05 g/mmol[d]	165/481 (34.3)

AAV, anti-neutrophil cytoplasmic autoantibody–associated vasculitis; ANCA, anti-neutrophil cytoplasmic autoantibody; eGFR, estimated glomerular filtration rate (Modified Diet in Renal Disease equation); ELISA, enzyme-linked immunosorbent assay; IQR, interquartile range; UPCR, urine protein-creatinine ratio.
[a]Serum creatinine at induction therapy initiation replaced by 800 μmol/l for 2 patients under renal replacement therapy; 3 missing values.
[b]eGFR at induction therapy initiation replaced by 5 ml/min per 1.73 m^2 for 2 patients under renal replacement therapy; 3 missing values.
[c]226 missing values for UPCR at induction therapy initiation.
[d]90 missing values for UPCR after induction therapy.
Quantitative values are given as median (IQR), and qualitative values are given as *n*/total *n* (%).

($n = 9$ of 316 [2.8%]) (adjusted sHR 4.62; 95% CI 2.08–10.28; $P < 0.001$) (cumulative incidence in Supplementary Figure S2). The only other factor associated with this outcome in multivariable analysis was higher sCreat after induction therapy (Supplementary Table S4).

Relapse and kidney relapse

During follow-up, 196 of the 571 patients (34.3%) experienced a subsequent relapse, of whom 42 had kidney relapses (7.4%). Thirteen patients developed kidney failure and 8 died before relapse occurrence. The median time from the end of induction to relapse, kidney failure, or death was 28 months (IQR 12–42 months).

In adjusted analysis for confounders with death and kidney failure as competing events, PR3-ANCA (vs. MPO-ANCA), maintenance therapies other than rituximab, and lower sCreat after induction therapy were the only factors associated with the overall risk of relapse (Table 3). Regarding the risk of kidney relapse, in adjusted analysis including non-kidney relapses as competing events, maintenance therapies other than rituximab, persistent hematuria, and UPCR ≥0.05 g/mmol after induction therapy were the sole significant prognostic factors identified (sHR 2.16; 95% CI 1.13–4.11; $P = 0.020$ and sHR 2.22; 95% CI 1.16–4.24; $P = 0.016$, respectively; Table 3). The results were similar after adjusting for ANCA persistence after induction therapy. ANCA persistence at this time point was not associated with the subsequent occurrence of any relapse, nor with kidney relapse. The cumulative incidence of kidney relapse according to persistent hematuria and UPCR is shown in Figures 3 and 4.

Subgroup analyses

In the subgroup of patients with kidney involvement at induction therapy initiation ($n = 441$ patients), the results were identical (Supplementary Figure S3 and Supplementary Tables S5 and S6).

In both subgroups of patients with MPO-ANCA and PR3-ANCA, death/kidney failure (observed in 14 of 185 and 12 of 318 cases, respectively) occurred more often in patients with UPCR ≥0.05 than in those with UPCR <0.05 g/mmol (Supplementary Table S7 and Supplementary Figures S4 and S5). For patients with PR3-ANCA, kidney relapses were more common in patients with UPCR ≥0.05 g/mmol. No other significant relationship between UPCR and hematuria after induction therapy and outcomes were found across MPO-ANCA and PR3-ANCA subgroups (Supplementary Table S7). ANCA persistence after induction was not associated with the subsequent occurrence of any relapse or kidney relapse within each subgroup.

Subgroup with kidney pathology

Initial kidney pathology data could be retrospectively collected for 65 patients included either in the RITUXVAS or the MAINRITSAN and MAINRITSAN2 trials and reclassified according to the glomerular histopathological classification currently used in AAV.[24] In this subgroup of patients with kidney involvement and available kidney biopsy results (detailed in Table 4), the focal subtype was the most frequently observed (23 of 65 [35%]) whereas the sclerotic subclass was less common (9 of 65 [14%]). The latest category was associated with more severely decreased GFR at the initial presentation and after the induction of remission as well as with higher UPCR levels at the end of induction therapy, but also with poor kidney prognosis, as almost

Table 2 | Bivariate and multivariable Cox regression analysis of factors associated with death or kidney failure

	Bivariate analysis		Multivariable analysis	
Variable	Hazard ratio (95% CI)	*P*	Adjusted hazard ratio (95% CI)	*P*
Male sex	0.86 (0.41–1.78)	0.67		
Older age (per 1-yr increase)	1.04 (1.01–1.08)	0.009	1.04 (1.00–1.07)	0.056
AAV type: MPA (vs. GPA)	3.10 (1.45–6.66)	0.004		
ANCA type (reference: PR3)				
MPO	2.36 (1.08–5.12)	0.030	1.09 (0.42–2.86)	0.107
Negative	1.53 (0.34–6.85)	0.578	0.85 (0.11–6.74)	0.877
Relapse (vs. *de novo* AAV flare)	0.62 (0.19–2.07)	0.441		
Kidney involvement	9.34 (1.27–68.68)	0.028		
Pulmonary involvement	0.32 (0.12–0.81)	0.017		
Intra-alveolar hemorrhage	1.08 (0.36–3.20)	0.894		
sCreat at induction therapy initiation (per 10 μmol/l)[a]	1.02 (1.01–1.03)	<0.001		
sCreat after induction therapy (per 10 μmol/l)	1.10 (1.08–1.13)	<0.001	1.11 (1.07–1.16)	<0.001
ANCA positive after induction therapy	0.85 (0.40–1.83)	0.683		
Maintenance therapy: other (vs. RTX)[b]	0.87 (0.42–1.83)	0.718	0.79 (0.32–1.97)	0.611
Hematuria after induction therapy	2.13 (1.01–4.49)	0.041	1.50 (0.62–3.62)	0.369
UPCR after induction therapy ≥0.05 g/mmol	7.91 (2.97–21.09)	<0.001	3.06 (1.09–8.59)	0.034
UPCR after induction therapy (per 0.1 g/mmol)	1.93 (1.61–2.30)	<0.001		

AAV, anti-neutrophil cytoplasmic autoantibody–associated vasculitis; ANCA, anti-neutrophil cytoplasmic autoantibody; CI, confidence interval; GPA, granulomatosis with polyangiitis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; PR3, proteinase 3; RTX, rituximab; sCreat, serum creatinine; UPCR, urine protein-creatinine ratio.
[a]sCreat at induction therapy initiation replaced by 800 μmol/l for 2 patients under renal replacement therapy.
[b]Other maintenance therapies: azathioprine ($n = 261$), mycophenolate mofetil ($n = 71$), none ($n = 27$).
Bivariate analysis: hazard ratios were obtained using the Cox proportional hazards model. Number of events: 29 (13 deaths, 16 kidney failure) in 571 patients.
Multivariable analysis: hazard ratios were obtained using the Cox proportional hazards model after adjustment for age, ANCA type, maintenance therapy, sCreat after induction therapy, hematuria, and UPCR ≥ 0.05 g/mmol after induction therapy. In the 417 patients included in this analysis, there were 24 events (death or kidney failure).

half of them met the composite death/kidney failure end point during follow-up. In contrast, patients with the focal subtype had very low levels of proteinuria and mildly decreased GFR after induction therapy, with an excellent prognosis, as only 4.3% of them reached the death/kidney failure end point.

The number of patients with available kidney pathology was too small to perform a multivariable analysis including both the glomerular classification and proteinuria. Nevertheless, after adjustment for the percentage of normal glomeruli, persistence of UPCR ≥0.05 g/mmol after induction therapy was still associated with the risk of death/severe CKD (HR 3.99; 95% CI 1.04–15.24; $P = 0.043$).

Other sensitivity analyses

A total of 3 variables included in the primary regression models had missing data (Supplementary Table S8). UPCR after induction therapy, the variable that had the largest amount of missing data, had 90 missing values (15.8%).

Multiple imputation was performed, and the imputed cohort included all 154 patients (27%) who were excluded because of missing values in any of the variables used in the regression models. The model estimate of UPCR ≥0.05 g/mmol for the risk of death/kidney failure from the imputed data set was consistent with the complete case cohort (vs. <0.05 g/mmol: adjusted HR 4.99; 95% CI 1.76–14.17; $P = 0.002$). However, missing data for UPCR and hematuria after induction therapy may not have been missing at random, a hypothesis that could limit the accuracy of this analysis.

In analyses with UPCR coded as a continuous variable, the prognostic value of persistent proteinuria was confirmed in multivariable analyses (Supplementary Table S9).

DISCUSSION

In this large cohort of 571 patients with AAVs, persistence of proteinuria after the induction of remission was an independent predictor of death/kidney failure whereas persistent hematuria or proteinuria after induction therapy were independent predictors of kidney relapse. On the basis of the individual patient data of 5 recent randomized controlled trials on AAV, this study is, to our knowledge, the largest one to investigate the prognostic value of persistence of proteinuria and hematuria after the induction of remission in this disease.

The long-term consequences of kidney involvement are a major concern in AAV. The severity of chronic kidney damage has mainly been associated with the level of sCreat/eGFR at diagnosis, reflecting the severity of the initial kidney insult and sometimes the diagnostic delay, which is necessary before therapy is initiated. Kidney survival can also be predicted by initial kidney pathology, and several studies have shown that both the percentage of sclerotic glomeruli and the degree of interstitial fibrosis/tubular atrophy are strongly associated with long-term kidney prognosis.[24,27,28]

Although the level of proteinuria at diagnosis has been associated with the presence of chronic glomerular lesions and unfavorable kidney outcome in unadjusted analyses,[29,30] little is known about the significance of persistent proteinuria at the end of induction therapy in AAV, in contrast to

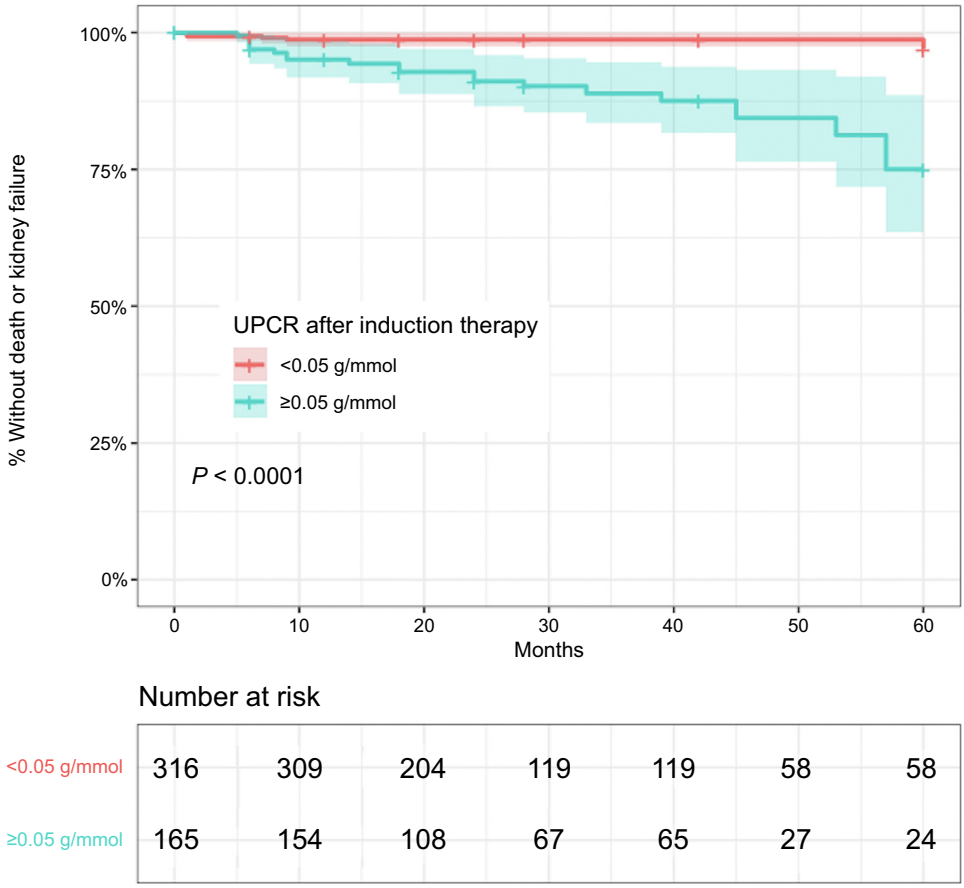

Figure 2 | Kaplan-Meier analysis of the composite outcome of death or kidney failure according to proteinuria after induction therapy (urine protein-creatinine ratio [UPCR] ≥0.05 or <0.05 g/mmol).

data observed in other glomerular diseases[16,17,31] as well as in cohorts with CKD.[14] Although patients with poor kidney outcome displayed higher proteinuria during follow-up in a small analysis of 21 patients with MPO-ANCA,[32] this result was not confirmed by de Joode *et al.*,[6] who analyzed 212 kidney AAVs and found no association between baseline or 6-month proteinuria and kidney failure. In their *post hoc* study of 149 patients extracted from the Wegener's Granulomatosis Etanercept Trial (WGET) and Rituximab for the Treatment of Wegener's Granulomatosis and Microscopic Polyangiitis (RAVE) trial,[18] Rhee *et al.* observed no significant effect of proteinuria at remission (assessed with a urine dipstick test) on eGFR slopes nor on the risk of subsequent relapse. Hence, our study is the first to demonstrate that UPCR ≥0.05 g/

Table 3 | Competing risk regression multivariable analysis of factors associated with any relapse and kidney relapse

	Any relapse			Kidney relapse		
Variable	Adjusted sHR	95% CI	*P*	Adjusted sHR	95% CI	*P*
Older age (per 1-yr increase)	0.99	0.98–1.00	0.070	1.02	0.99–1.04	0.170
ANCA type (reference: MPO)						
Negative	1.51	0.77–2.93	0.230	1.27	0.32–4.95	0.730
PR3	1.67	1.15–2.43	0.007	1.40	0.68–2.88	0.360
Maintenance therapy: other (vs. RTX)	3.80	2.44–5.91	<0.001	7.11	2.15–23.52	0.001
sCreat after induction therapy (per 10 μmol/l)	0.94	0.89–0.99	0.013	0.98	0.94–1.03	0.490
Hematuria after induction therapy	1.01	0.70–1.45	0.970	2.16	1.13–4.11	0.020
UPCR after induction therapy ≥0.05 g/mmol	1.06	0.73–1.54	0.750	2.22	1.16–4.24	0.016

ANCA, anti-neutrophil cytoplasmic autoantibody; CI, confidence interval; MPO, myeloperoxidase; PR3, proteinase 3; RTX, rituximab; sCreat, serum creatinine; sHR, sub-distribution hazard ratio; UPCR, urine protein-creatinine ratio.
sHRs were obtained using Fine and Gray competing risk regression after adjustment for each of the variables presented in this table. Sensitivity analyses also adjusted for ANCA persistence after induction therapy did not change the results. Of the 417 patients included in these analyses, 141 underwent relapses, 36 underwent kidney relapses, and 17 had a competing event occurring before relapse (11 kidney failure, 6 deaths). For kidney relapse analysis, non-kidney relapses were also considered as competing events.

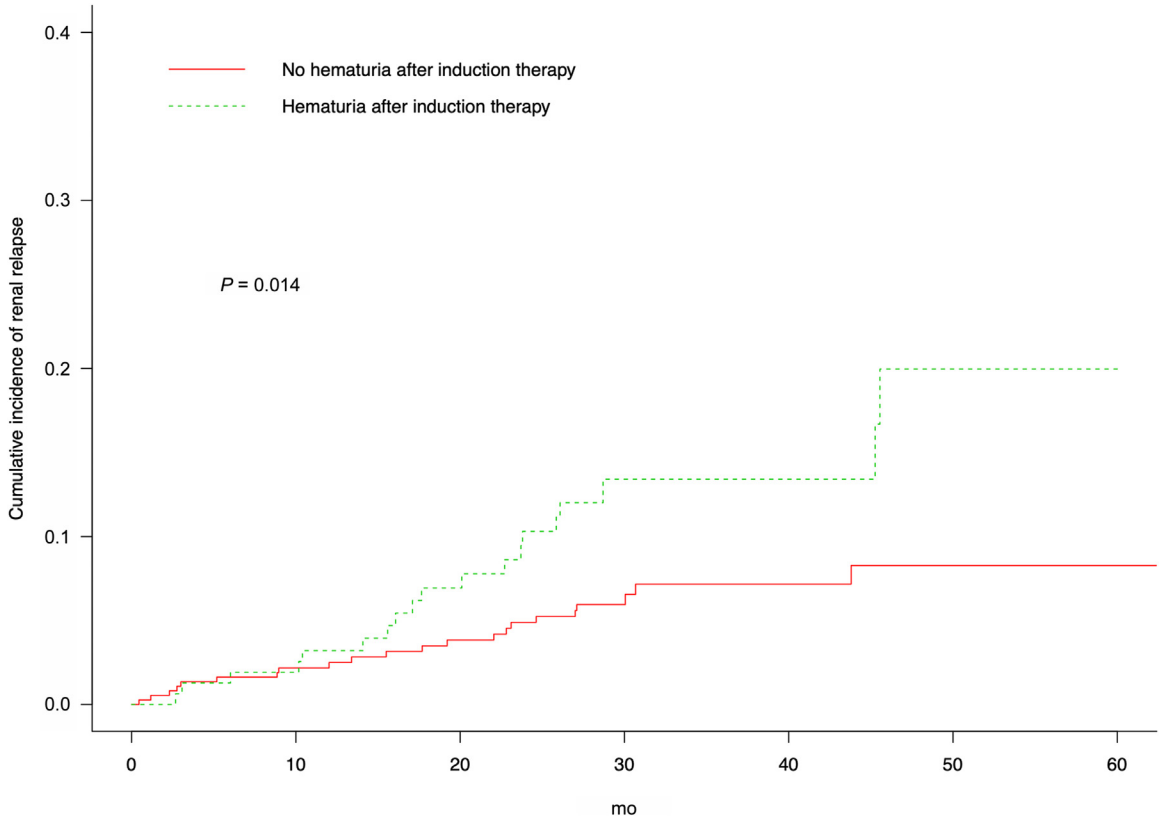

Figure 3 | Cumulative incidence of kidney relapse according to persistent hematuria after induction therapy. Competing risk survival model: the event of interest was kidney relapse, and the competing events were death and non-kidney relapses.

mmol after induction therapy is a strong predictor (HR 3) for the clinically meaningful composite outcome of death or kidney failure even after adjustment for age, ANCA type, type of maintenance therapy, and kidney function after induction. This association was found in all subgroups of patients and was consistent in sensitivity analyses, including multiple imputation for missing data. The precise significance of persistent proteinuria remains unclear as it might be associated either with resistant and still active glomerulonephritis or with chronic kidney damage due to glomerular scarring, such as fibrotic crescents and sclerotic glomeruli.[33,34] Nevertheless, the fact that persistent proteinuria after induction therapy was also associated with the occurrence of subsequent kidney relapse (sHR 2.22 in adjusted analyses) supports the hypothesis that proteinuria may reflect the ongoing inflammatory activity. Data from studies evaluating the anti-inflammatory complement inhibitor avacopan in AAV are consistent with this hypothesis, as proteinuria excretion rate fell more quickly than in standard-of-care treated patients, and this was associated with higher subsequent GFR.[35] Although the prognostic value of the initial kidney biopsy is well established in AAV,[24,27] a systematic assessment of repeat biopsies to detect ongoing glomerular inflammation and guide clinical management is currently lacking. Considering the poor clinical-pathological correlation recently underlined in lupus nephritis,[36,37] similar studies would be of special interest in AAV, especially in patients with persistence of proteinuria and/or hematuria, after induction therapy is achieved.

In addition, our data indicate that the presence of hematuria after induction therapy was an independent predictive factor for the risk of kidney relapse (sHR 2.16) and confirm the findings of 2 recent studies. In the analysis by Rhee *et al.*,[18] an increase in hematuria extent was associated with a higher 12-month risk of kidney relapse. In a retrospective French study of 86 patients,[38] hematuria at remission was associated with an increased kidney relapse risk within 44 months. Again, the pathophysiological significance of the persistence of isolated hematuria in patients otherwise in clinical remission is uncertain. Histopathological data of patients in such situations are scarce, and the only small series of repeat kidney biopsies published to date did not find correlations between hematuria and histological activity.[38–41] Of note, our data suggest that the overall—kidney and extra-kidney—relapse risk was not predicted by urinalysis but was higher in patients with PR3-ANCA, in those with better kidney function, and in those who did not receive rituximab as maintenance therapy, as previously described.[42–45] Pulmonary involvement and ANCA persistence after induction therapy, previously identified as risk factors for relapses,[43,46] were not highlighted as such in our multivariable analysis. Although there was an association between persistent hematuria and

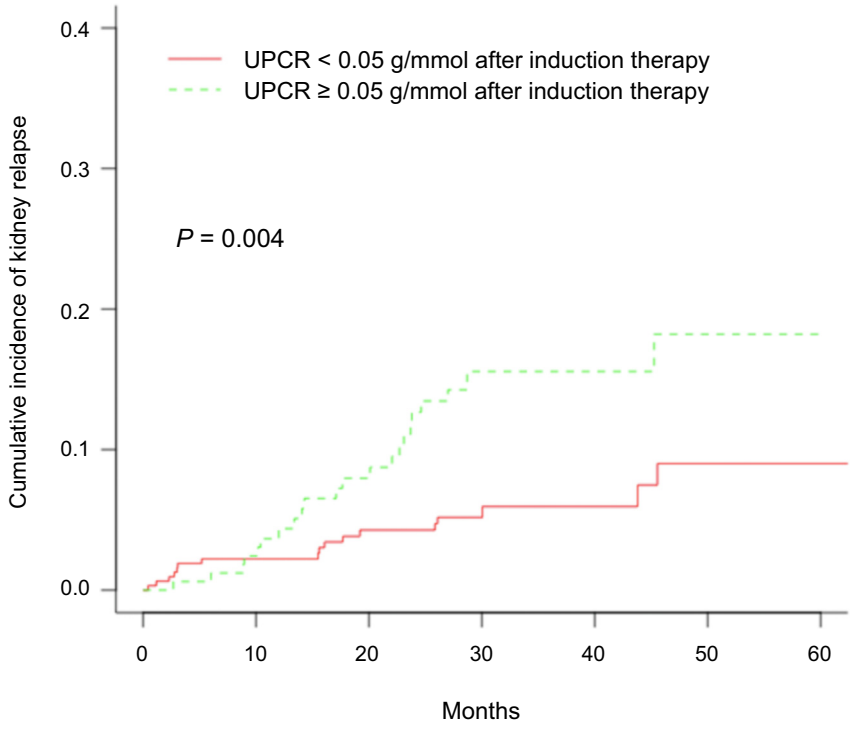

Figure 4 | Cumulative incidence of kidney relapse according to persistent urine protein-creatinine ratio (UPCR) ≥0.05 g/mmol after induction therapy. Competing risk survival model: the event of interest was kidney relapse, and the competing events were death and non-kidney relapses.

risk of death/kidney failure in bivariate analysis, this relationship was not significant after adjusting for confounders. Similarly, maintenance therapy with rituximab, which was clearly associated with a reduced risk of kidney (and overall) relapse, was not predictive of kidney survival, perhaps owing to a lack of power.

Table 4 | Characteristics at induction therapy initiation and after induction therapy and outcomes according to initial kidney biopsy (Berden classification[24])

Variable	Focal (n = 23)	Crescentic (n = 16)	Mixed (n = 17)	Sclerotic (n = 9)	Total (n = 65)
Age, yr	61 (53–71)	58 (52–64)	67 (60–74)	54 (48–61)	61 (52–69)
MPO vs. PR3	8 vs. 15	3 vs. 13	11 vs. 6	6 vs. 3	28 vs. 37
sCreat at induction therapy initiation[a]	111 (94–194)	406 (318–555)	187 (128–275)	388 (317–464)	243 (115–388)
sCreat after induction	106 (95–117)	131 (113–173)	135 (108–200)	228 (168–286)	124 (105–180)
UPCR after induction (g/mmol)	0.029 (0.004–0.044)	0.130 (0.042–0.200)	0.067 (0.030–0.110)	0.129 (0.099–0.195)	0.051 (0.021–0.130)
UPCR after induction ≥0.05 g/mmol	5/22 (22.7)	11/15 (73.3)	9/17 (52.9)	8/9 (88.9)	33/63 (52.4)
Hematuria after induction	7/22 (31.8)	7/16 (43.8)	9/17 (52.9)	2/7 (28.6)	25/62 (40.3)
Death or kidney failure	1/23 (4.3)	1/16 (6.3)	3/17 (17.6)	4/9 (44.4)	9/65 (5.1)
	Reference	HR 1.58 (95% CI 0.09–25.20)	HR 5.27 (95% CI 0.54–51.10)	HR 9.21 (95% CI 1.02–82.71)	
Death or severe CKD[b]	3/23 (13.0)	1/16 (6.3)	6/17 (35.3)	7/9 (77.8)	17/65 (26.2)
	Reference	HR 0.50 (95% CI 0.05–4.79)	HR 3.60 (95% CI 0.89–14.49)	HR 6.48 (95% CI 1.67–25.18)	
Any relapse	10/23 (43.5)	5/16 (31.3)	5/17 (29.4)	2/9 (22.2)	22/65 (33.8)
	Reference	sHR 0.64 (95% CI 0.21–1.91)	sHR 0.86 (95% CI 0.30–2.46)	sHR 0.30 (95% CI 0.07–1.28)	
Kidney relapse	0/23 (0)	3/16 (18.8)	3/17 (17.6)	1/9 (11.1)	7/65 (10.8)

CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IQR, interquartile range; MPO, myeloperoxidase; PR3, proteinase 3; sCreat, serum creatinine; sHR, subdistribution hazard ratio; UPCR, urine protein-creatinine ratio.
[a]sCreat at induction therapy initiation replaced by 800 μmol/l for 1 patient under renal replacement therapy.
[b]Severe CKD: eGFR <30 ml/min per 1.73 m^2.
Quantitative values are given as median (IQR), and qualitative values are given as n/total n (%).
HRs were obtained using the Cox unadjusted proportional hazards model.
sHRs were obtained using unadjusted Fine and Gray competing risk regression.

Our study has several limitations. First, kidney involvement was not present in all patients, and one could argue that persistent proteinuria is just the reflection of unspecific kidney disease at presentation, a condition known to be associated with a long-term kidney failure risk. Nevertheless, when focusing on patients with kidney vasculitis, our results were not modified, meaning that persistent proteinuria allows differentiation between patients with low- and high-risk kidney AAVs. Second, our results cannot be applied to all patients with AAV. Indeed, patients included in this study were mostly of European ancestry, and only a minority of them received rituximab (15% for induction, 37% for maintenance), an immunosuppressive drug that is now considered as standard-of-care therapy in AAV. Third, we performed *post hoc* analyses of heterogeneous randomized controlled trials with different induction/maintenance immunosuppressive schemes, inclusion criteria, and end points. However, data, including outcome assessment, were prospectively collected, with the exception of proteinuria, obtained retrospectively in the MAINRITSAN trial. Fourth, proteinuria and hematuria evaluations relied on single measurement—fluctuations in urine findings might occur between several samples—and 24-hour proteinuria or spot UPCR was used indistinctly to estimate proteinuria (converted in UPCR for all). However, potential misclassification induced bias would probably not be differential. In addition, the glomerular origin of hematuria could not be certified as the presence of urinary casts or acanthocytes was not available, nor was the intensity of hematuria. Finally, we could not include in our models important missing covariates such as prescription of renin-angiotensin-system blockers, which can modify both the level of proteinuria and kidney prognosis, as well as initial kidney biopsy results, which could only be retrospectively obtained for a small proportion of our study population. However, our data suggest that persistence of proteinuria after induction therapy was particularly elevated in patients with the sclerotic subtype of the glomerular AAV classification, which is also known to have worse long-term kidney prognosis. Furthermore, persistent proteinuria was predictive of kidney outcome, irrespective of the initial percentage of normal glomeruli.

Our results have important implication for clinical research, as they suggest that persistent proteinuria could be considered as a target in future AAV studies. Nevertheless, further studies are needed to demonstrate that resolution of proteinuria can be used as a short-term surrogate marker. Indeed, the identification of a strong but simple prognostic factor assessed after induction therapy could provide a valuable surrogate end point to evaluate future therapies. Despite validation of surrogate end points based on proteinuria reduction in different types of glomerulonephritis,[47,48] this approach has never been validated in AAV.[49] Although we know that a significant proportion of patients with AAV reaching kidney failure have slowly progressive CKD without active vasculitis,[50] no specific study has been performed to demonstrate that nephroprotection with antiproteinuric treatments such as renin-angiotensin-system inhibitors can modify kidney prognosis in AAV-related nephropathy.

We believe that our findings can be useful for guiding clinical care of patients with AAV. Individualized management could embed closer follow-up and longer duration of maintenance therapy for patients at a higher risk of relapse, including those with PR3-ANCA, persistent ANCA positivity, or persistent hematuria/proteinuria. Pending for more accurate insight into the significance of persistent proteinuria, increased kidney risk in this subgroup of patients emphasizes the need for careful nephroprotective measures such as renin-angiotensin-system blockers or sodium-glucose-transporter 2 inhibitors prescription, therapeutic interventions that has been proven particularly useful in other glomerulopathies.[51–53]

Precision medicine relying on individual characteristics is currently revolutionizing patient management in many fields of medicine. Awaiting for the development and validation of novel biomarkers,[54] simple, noninvasive, and costless assessment of proteinuria and hematuria should be used for the management of AAV glomerulonephritis, especially to assess the long-term kidney prognosis of these patients.

DISCLOSURE

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(MAINRITSAN2),[21] RITUXVAS (An international, randomised, open label trial comparing a rituximab-based regimen with a standard cyclophosphamide/azathioprine based regimen in the treatment of active, generalised anti-neutrophilic cytoplasmic antibodies associated vasculitis),[3] Clinical Trial of Mycophenolate Versus Cyclophosphamide in ANCA Vasculitis (MYCYC),[22] and Mycophenolate Mofetil Versus Azathioprine for Maintenance Therapy in ANCA Associated Systemic Vasculitis (IMPROVE).[19] In particular, the authors thank Christian Pagnoux, Chahera Kouatra, Olivier Aumaître, Pascal Cohen, François Maurier, Olivier Decaux, Jacques Ninet, Pierre Gobert, Thomas Quémeneur, Claire Blanchard-Delaunay, Pascal Godmer, Xavier Puéchal, Pierre-Louis Carron, Pierre-Yves Hatron, Nicolas Limal, Mohamed Hamidou, Maize Ducret, Eric Daugas, Thomas Papo, Bernard Bonnotte, Alfred Mahr, and Philippe Ravaud; Elodie Perrodeau, Stanislas Faguer, Antoine Huart, Christian Agard, Maxime Samson, Noémie Jourde-Chiche, François Lifermann, Catherine Hanrotel-Saliou, Nicolas Martin-Silva, Grégory Pugnet, Marie Matignon, Jean-François Viallard, François Maurier, Nadine Meaux-Ruault, Sophie Rivière, and Jean Sibilia; Michael Walsh, Caroline O. Savage, Kirsten de Groot, Lorraine Harper, Thomas Hauser, Irmgard Neumann, Vladimir Tesar, Karl-Martin Wissing, and Wilhelm Schmitt; Jose Ballarin, Daniel Engelbert Blockmans, Paul Brogan, Annette Bruchfeld, Maria C. Cid, Karen Dahlsveen, Janak de Zoysa, Georgina Espigol-Frigolé, Peter Lanyon, Chen Au Peh, Augusto Vaglio, Dorothy Walsh, and Giles Walters; and Jan Willem Cohen Tervaert, Raashid Luqmani, Matthew D. Morgan, Marten Segelmark, Pieter van Paassen, and Kerstin Westman. The author also thank the French Vasculitis Study Group (FVSG) and European Vasculitis Society (EUVAS) for their support.

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SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Table S1. Studies' characteristics.

Supplementary Table S2. Characteristics at the initiation of and after induction therapy according to trial (for the 571 patients included).

Supplementary Table S3. Multivariable Cox regression analysis of factors associated with the composite outcome of death or severe chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR] $<$30 ml/min per 1.73 m^2).

Supplementary Table S4. Competing risk regression analysis of factors associated with severe chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR] $<$30 ml/min per 1.73 m^2), with death as a competing event.

Supplementary Table S5. Multivariable Cox regression analysis of factors associated with the composite outcome of death or kidney failure in patients with kidney involvement.

Supplementary Table S6. Competing risk regression analysis of factors associated with any relapse and kidney relapse in patients with kidney involvement.

Supplementary Table S7. Outcomes according to urine protein-creatinine ratio (UPCR) and hematuria after induction therapy across myeloperoxidase (MPO)–anti-neutrophil cytoplasmic antibody (ANCA) and proteinase 3 (PR3)–ANCA subgroups in unadjusted analyses.

Supplementary Table S8. Description of the variables with missing data.

Supplementary Table S9. Multivariable Cox regression analysis of factors associated with death or kidney failure, with urine protein-creatinine ratio (UPCR) after induction therapy as a continuous variable.

Supplementary Figure S1. Cumulative incidence curves for kidney failure according to proteinuria after induction therapy (urine protein-creatinine ratio [UPCR] $\geq$0.05 or $<$0.05 g/mmol). Competing risk survival model: the event of interest was kidney failure, and the competing event was death.

Supplementary Figure S2. Cumulative incidence curves for severe chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR] $<$30 ml/min per 1.73 m^2) according to proteinuria after induction therapy (urine protein-creatinine ratio [UPCR] $\geq$0.05 or $<$0.05 g/mmol). Competing risk survival model: the event of interest was incident eGFR $<$30 ml/min per 1.73 m^2 (including kidney failure), and the competing event was death.

Supplementary Figure S3. Kaplan-Meier analysis of the composite outcome of death or kidney failure according to proteinuria after induction therapy (urine protein-creatinine ratio [UPCR] $\geq$0.05 or $<$0.05 g/mmol) in patients with kidney involvement.

Supplementary Figure S4. Kaplan-Meier analysis of the composite outcome of death or kidney failure according to proteinuria after induction therapy (urine protein-creatinine ratio [UPCR] $\geq$0.5 or $<$0.05 g/mmol) in patients with myeloperoxidase (MPO)–anti-neutrophil cytoplasmic antibody (ANCA).

Supplementary Figure S5. Kaplan-Meier analysis of the composite outcome of death or kidney failure according to proteinuria after induction therapy (urine protein-creatinine ratio [UPCR] $\geq$0.05 or $<$0.05 g/mmol) in patients with proteinase 3 (PR3)–anti-neutrophil cytoplasmic antibody (ANCA).

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